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Maintained serum sodium in male ultra-marathoners : the role of fluid intake, vasopressin, and aldosterone in fluid and electrolyte regulation — Source link

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Abstract: Exercise-associated hyponatremia (EAH) is a well know electrolyte disorder in endurance athletes. Although fluid overload is the most like etiology, recent studies, however, argued whether EAH is a disorder of vasopressin secretion. The aims of the present study were to investigate (i) the prevalence of EAH in male ultra-marathoners and (ii) whether fluid intake, aldosterone or vasopressin, as measured by copeptin, were associated with post-race serum sodium concentration ([Na+]). In 50 male ultra-marathoners in a 100 km ultra-marathon, serum [Na+], aldosterone, copeptin, serum and urine osmolality, and body mass were measured pre- and post-race. Fluid intake, renal function parameters and urine excretion were measured. No athlete developed EAH. Copeptin and aldosterone increased; a significant correlation was found between the change in copeptin and the change in serum [Na+], no correlation was found between aldosterone and serum [Na+]. Serum [Na+] increased by 1.6%; body mass decreased by 1.9 kg. The change in serum [Na+] and body mass correlated significantly and negatively. The fluid intake of 0.58 l/h was positively related to the change in body mass and negatively to both post-race serum [Na+] and the change in serum [Na+]. We conclude that serum [Na+] was maintained by both the mechanisms of fluid intake and the hormonal regulation of vasopressin.

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Maintained serum sodium in male ultra-marathoners – the role of fluid intake, vasopressin and aldosterone in fluid and electrolyte regulation

Fluid metabolism in ultra-marathoners

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ABSTRACT

Exercise-associated hyponatremia (EAH) is a well know electrolyte disorder in endurance athletes. Although fluid overload is the most like etiology, recent studies, however, argued whether EAH is a disorder of vasopressin secretion. The aims of the present study were to investigate (*i*) the prevalence of EAH in male ultra-marathoners and (*ii*) whether fluid intake, aldosterone or vasopressin, as measured by copeptin, were associated with post-race serum sodium concentration ($[Na^+]$). In 50 male ultra-marathoners in a 100-km ultra-marathon, serum $[Na^+]$, aldosterone, copeptin, serum and urine osmolality, and body mass were measured pre and post-race. Fluid intake, renal function parameters and urine excretion were measured. No athlete developed EAH. Copeptin and aldosterone increased; a significant correlation was found between the change in copeptin and the change in serum $[Na^+]$, no correlation was found between aldosterone and serum $[Na^+]$. Serum $[Na^+]$ increased by 1.6 %; body mass decreased by 1.9 kg. The change in serum $[Na^+]$ and body mass correlated significantly and negatively. The fluid intake of ~0.58 L/h was positively related to the change in body mass and negatively to both post-race serum $[Na^+]$ and the change in serum $[Na^+]$. We concluded that serum $[Na^+]$ was maintained by both the mechanisms of fluid intake and the hormonal regulation of vasopressin.

Key words: electrolytes, aldosterone, vasopressin, ultra-endurance

INTRODUCTION

Exercise-associated hyponatremia (EAH) is a well known and frequently discussed electrolyte disorder in endurance athletes [1-4]. EAH is defined as serum sodium concentration ($[Na^+]$) < 135 mmol/l during exercise or up to 24 hours after exercise [2, 5-7]. Most athletes with EAH are asymptomatic [8] or show mild symptoms [7, 9, 10]. In runners, the prevalence of EAH seems to be dependent on the duration of performance and can vary between 9 % and 51.2 % [1, 5, 11]. Risk factors for EAH are long duration of exercise, female sex, excessive fluid consumption during exercise, intake of non-steroidal anti-inflammatory drugs, a slow running pace and unusually hot or extremely cold temperatures [6, 10, 12]. There is an inverse linear relationship between a marathon race time and serum $[Na^+]$, where runners with longer race times had lower serum $[Na^+]$ [9]. Fluid overload is considered as the main risk factor in the pathogenesis of EAH [1, 6, 7, 10, 12, 13]. Several studies described correlations between an increase in body weight and a decrease of serum $[Na^+]$ [3, 14, 15, 16, 17].

In recent years, however, it was hypothesized that the hormone vasopressin could be involved in the pathogenesis of EAH in endurance athletes, [2, 14] and there have been athletes described as having EAH who were unable to urinate [2]. A sufficient activity of vasopressin to suppress the production of urine and to inhibit water loss via the kidney would explain the absent urination. This phenomenon, however, was also noticed in runners with EAH but without measurable vasopressin levels. However, the half-life period of vasopressin is very short, the hormone is unstable and its detection is difficult. This could be one reason for missing the detection of vasopressin influences [18].

Apart from vasopressin, the hormone aldosterone was also believed to be responsible for water retention [19]. Milledge *et al.* described an increased plasma aldosterone concentration,

an increased renin activity and demonstrated a constant serum [Na^+] in a 5-day hill walking event [19]. Aldosterone was suggested as the main cause of the extracellular volume expansion through activation of the renin-angiotensin-aldosterone system [19]. Another study of an ultra-endurance race over 161 km described a decrease of serum [Na^+] with no case of EAH and a significant increase in both vasopressin and aldosterone [13].

There seems to be a conflict in the actual discussion as to whether EAH is due to fluid overload or an increased activity of vasopressin in endurance athletes [14, 20]. Following Noakes, three independent mechanisms explain why some athletes develop EAH during and after prolonged exercise: (*i*) overdrinking due to biological or psychological factors; (*ii*) inappropriate secretion of vasopressin, in particular, the failure to suppress vasopressin secretion in the face of an increase in total body water; and (*iii*) a failure to mobilize Na^+ from the osmotically inactive sodium stores or alternatively inappropriate osmotic inactivation of circulating Na^+ [16]. The problem is to identify those athletes with inappropriate secretion of vasopressin, especially in the regulation of body water in those who overdrink. In some athletes, there is an appropriate diuresis so that they do not gain weight or if they do, they manage to maintain their serum [Na^+] perhaps by mobilizing sodium from internal stores. However, in the other athletes, the appropriate diuresis does not occur thus leading to fluid retention and EAH.

The aim of the present study was, therefore, to investigate whether fluid intake, electrolyte intake or fluid regulating hormones, such as aldosterone or vasopressin, were associated with post-race serum [Na^+]. We hypothesized that both fluid intake and changes in vasopressin, as suggested in a recent study of Hew-Butler *et al.* [14], and aldosterone responsible for fluid retention [19] were involved in the pathogenesis of EAH. This study is different from former studies since vasopressin was quantified by its co-secreted peptide copeptin. While readily

degraded *in vivo*, copeptin is stable for a number of days after blood sampling, in contrast to vasopressin, and is also easier to analyse [18].

MATERIALS AND METHODS

The subjects

The organizer of the '100 km Lauf' in Biel, Switzerland, contacted all participants of the 2010 race three months before the start via a separate newsletter and informed them about the planned investigation. Fifty-six male ultra-runners volunteered to participate in the study, 50 athletes finished the race successfully within the time limit of 21 hours. Two non-finishers reported about overuse injuries of the lower limbs, four non-finishers were not able to finish the race due to muscular problems. The characteristics of anthropometry, training and previous experience are represented in **Table 1**. The study was approved by the Institutional Review Board for use of Human subjects of the Canton of Zurich, Switzerland, and all the study subjects gave their informed written consent.

The race

The race took place on June 11, 2010. The athletes started the race at 10:00 p.m. They had to climb a total altitude of 645 metres. During these 100 km, the organizer provided a total of 17 aid stations offering an abundant variety of food and beverages such as hypotonic sports drinks, tea, soup caffeinated drinks, water, bananas, oranges, energy bars and bread. The athletes were allowed to be supported by a cyclist in order to have additional food and clothing, if necessary. The temperature at the start was 21.7 °C, dropped to 15.6 °C during the night and rose to 18.1 °C the next day. Humidity was 52% at the start, rose to 62% during the night and to 69% the next day. Barometric pressure was 1007.8 hPa at the start, rose to 1011.0 hPa in the night and was constant at 1011.9 the next day.

Measurements and Calculations

Between 05:00 and 10.00 p.m. on race day, pre-race measurements were performed. Body mass was measured using a commercial scale (Beurer BF 15, Beurer GmbH, Ulm, Germany) to the nearest 0.1 kg after the bladder was emptied. Venous blood samples were drawn in a sitting position and urine samples were collected. Two Sarstedt S-Monovettes (serum gel, 7.5 ml) for chemical and one Sarstedt S-Monovette (EDTA, 2.7 ml) (Sarstedt, Nümbrecht) for haematological analysis were drawn. Monovettes for serum and plasma were centrifuged at 3,000 g for 10 min at 4 °Celsius and then stored on ice. Urine was collected in Sarstedt monovettes for urine (10 ml). Blood and urine samples were transported immediately after collection to the laboratory and were analysed within six hours. In the venous blood samples, haemoglobin, haematocrit, $[Na^+]$, $[K^+]$, creatinine, urea, and osmolality were measured. Haematologic parameters were determined using ADVIA® 120 (Siemens Healthcare Diagnostics, Deerfield, IL, USA). Serum parameters were measured using COBAS INTEGRA® 800 (Roche, Mannheim, Germany). Osmolality of serum and urine samples was determined using Fiske® Modell 210 Mikro-Osmometer (IG Instrumenten-Gesellschaft AG, Zurich, Switzerland). In the urine samples, creatinine, urea, $[Na^+]$, $[K^+]$, urine specific gravity and osmolality were determined. Specific gravity was analysed using a Clinitek Atlas® Automated Urine Chemistry Analyzer (Siemens Healthcare Diagnostics, Deerfield, IL, USA). Creatinine and urea were measured using a COBAS INTEGRA® 800. Electrolytes were determined using an ISE IL 943 Flame Photometer (GMI, Inc., Ramsey, MN, USA). Because we did not know the time or volume of urine collection, we expressed urine concentrations as fractional excretions. This applied to the following parameters: Sodium, potassium, urea, osmolality. We used the formula: Fractional excretion of *parameter* = $((Parameter_{Urine} \times Creatinine_{Serum})/(Parameter_{Serum} \times Creatinine_{Urine})) \times 100$ following Espinel [21]. Transtubular potassium gradient was calculated using the equation: Transtubular potassium gradient = $(Potassium_{Urine} \times Osmolality_{Serum})/(Potassium_{Serum} \times Osmolality_{Urine})$ according to

West *et al*. [22]. The percentage change in plasma volume was estimated following Strauss *et al*. [23]. Aldosterone was measured by RIA (Radio Immuno Assay) using a Gamma-Counter 1277 (DRG Instruments GmbH, Germany). Copeptin was analysed using TRACE (Time Resolved Amplified Kryptat Emssion) with Kryptor (BRAHMS GmbH, Germany). Immediately after arrival at the finish line, identical measurements were taken. Upon arrival at the post-race measurement, the athletes were asked for symptoms of EAH [7, 9, 10,].

Between the pre-race and the post-race measurements, the athletes recorded their intake of food and drink using paper and pencil. At each aid station, they noted both the kind and amount of food and fluid ingested. At these aid stations, liquids and food were prepared in a standardized manner, i.e. beverages and food were provided in standardized size portions. The drinking cups were filled to 0.2 l, the energy bars and the fruits were halved. The athletes had only to mark at which station they consumed liquids and food. They also recorded additional food and fluid intake provided by the support crew as well as the intake of salt tablets and other supplements. The composition of fluids and solid food were assessed using a food table [24]. The day before the start of the race, during the race, and the three days after the race, the athletes recorded their urine excretion at each micturition using a graduated jug to the nearest 0.1 l. After the race, finishers and non-finishers were asked for symptoms of EAH such as weakness, confusion, headache, nausea or vomiting [10].

Statistical Analysis

Data are presented as mean values and 95% CI. Pre and post-race results were compared using paired T-test. A Pearson correlation analysis was used to check for associations between parameters with statistically significant changes, and linear regression for the regression line in Figures 1 to 5. For a better fit of normal distribution, the following parameters were

logarithmically transformed: Plasma aldosterone and copeptin levels, and urine potassium-to-sodium ratio. Statistical significance was accepted with $p < 0.05$ (two-sided hypothesis).

RESULTS

Fifty of the 56 study participants successfully finished the race within the time limit of 21 hours. Their training and previous experience is represented in **Table 1**. Weekly running kilometres ($r = -0.28$; $p = 0.0473$), running speed during training ($r = -0.58$; $p < 0.0001$), personal best time in a marathon ($r = 0.61$, $p < 0.0001$) and personal best time in a 100 km ultra-marathon ($r = 0.80$; $p < 0.0001$) were related to race time. Their race time was 12:15 (11:51;12:47) h:min, corresponding to a mean speed of 8.4 (8.0;8.7) km/h.

Body mass decreased by 1.9 kg (- 2.5 %) (see **Table 2**). Haemoglobin and haematocrit remained constant, calculated plasma volume increased by 1.0 (-1.2;3.2) % (n.s). Serum osmolality increased by 1.9 % ($p < 0.0001$). Serum sodium increased by 1.6 % ($p < 0.0001$) whereas serum potassium remained constant. In two athletes serum [Na^+] was, both pre- and post-race, < 135 mmol/l. In one subject, serum [Na^+] dropped from 133 mmol/l pre- race to 132 mmol/l post-race; in the other subject, serum [Na^+] increased from 131 mmol/l pre-race to 133 mmol/l post-race. For all 50 finishers, fractional sodium excretion decreased, fractional potassium excretion increased, fractional urea excretion decreased, fractional osmolar excretion decreased and transtubular potassium gradient increased.

The changes in body mass were significantly and negatively related to post-race serum [Na^+] (see **Figure 1**). The increase in plasma osmolality was highly significantly associated with both the increases in serum urea ($r = 0.71$, $p < 0.0001$) and serum [Na^+] ($r = 0.51$, $p < 0.0001$). The increase in urine osmolality was highly significantly related to the increase in urine urea ($r = 0.77$, $p < 0.0001$) and to the decrease in urine [Na^+] ($r = 0.57$, $p < 0.0001$).

The athletes consumed 7.3 (6.6;7.9) l of fluid during the 100 km, equal to 8.1 (7.7;8.9) ml · h^{-1}· kg^{-1} and 0.072 (0.066; 0.078) l/km, respectively. Regarding electrolytes they ingested 7.1 (5.6; 8.6) mg of sodium/h^{-1}· kg^{-1} and 2.4 (2.1; 2.8) mg of potassium /h^{-1}· kg^{-1}, equal to 5.22 (4.14; 6.30) mg sodium/km and 1.79 (1.55; 2.03) mg potassium/km, respectively. Energy intake was 3.2 (2.6;3.9) kcal· h^{-1}· kg^{-1}, equal to 29.2 (23.2; 35.3) kcal/km. Fluid intake was significantly and positively related to the change in body mass ($r = 0.40$, $p = 0.004$). Also, fluid intake was significantly and negatively related to both post-race serum [Na^+] (see **Figure 2**) and the change in serum [Na^+] ($r = - 0.38$, $p = 0.0072$). Sodium intake was neither related to post-race serum [Na^+] nor to the change in serum [Na^+]. Fluid intake was neither related to post-race copeptin concentration nor to the change in copeptin. Also, fluid intake correlated neither to post-race aldosterone concentration nor to the change in aldosterone.

Copeptin and aldosterone increased highly significantly. There was a mild to moderate association between the change in serum osmolality and copeptin (see **Figure 3**) and between copeptin and urine osmolality (see **Figure 4**). The change in copeptin was related to the change in serum [Na^+] ($r = 0.36$, $p = 0.01$); post-race copeptin was not associated with post-race serum [Na^+]. Post-race copeptin concentration and the change in copeptin concentration were not related to running speed during the race. The change in aldosterone was highly significantly and positively associated with post-race transtubular potassium gradient ($r = 0.37$, $p = 0.0078$) and the change in potassium-to-sodium ratio in urine (see **Figure 5**). Post-race aldosterone concentration ($r = 0.36$, $p = 0.0110$) and the change in aldosterone concentration ($r = 0.38$, $p = 0.0065$) were, however, both significantly and positively related to running speed during the race. Post-race aldosterone was not related to post-race serum [Na^+]; also the change in aldosterone was not associated with the change in serum [Na^+].

The athletes recorded 5.6 (4.5;6.6) micturitions and voided a total of 1.5 (1.2;1.8) l of urine during the race, equal to 1.6 (1.3) ml · h^{-1}· kg^{-1}. Urine excretion was significantly increased during the race compared to pre-race, was reduced post-race and reached pre-race levels only on Day 3 after the race (see **Figure 6**). The change in copeptin was neither related to the number of urinations nor to urine excretion during the race. No athlete reported symptoms of EAH such as weakness, confusion, headache, nausea or vomiting upon arrival after the race.

DISCUSSION

The aim of the present study was to assess whether fluid or electrolyte intake, or fluid and electrolyte regulating hormones such as vasopressin and aldosterone, were associated with post-race serum [Na^+] in order to describe a potential mechanism for EAH. We hypothesized that both mechanisms would be involved in the pathogenesis of EAH. No athlete developed EAH; post-race serum [Na^+] was associated with fluid intake and the change in copeptin was correlated to the change in serum [Na^+]. No association was found between serum [Na^+] and aldosterone.

Prevalence of exercise-associated hyponatremia in ultra-marathoners

No subject developed EAH. Two athletes showed serum [Na^+] <135 mmol/l both pre and post-race. However, since both subjects already had a pre-race serum [Na^+] of <135 mmol/l, no EAH occurred by definition. Forty-eight runners with serum [Na^+] >135 mmol/l pre-race finished the race with serum [Na^+] in the normal range. The prevalence of EAH varies considerably in the literature on runners [1, 5, 6, 8, 11, 25]; with a 9 % prevalence of EAH in a 90-km ultra-marathon [1], and up to a 22 % prevalence of EAH reported from the Houston marathon [9]. In a 24-hour ultra-run, no case of EAH occurred [25], and in a 100-km ultra-marathon, the prevalence of EAH was ~5% [8]. In a review where the data of 2,135 athletes was analysed, the prevalence of EAH was 7 % [16]. However, in a recent study at the 'Rio del Lago 161 km endurance run', Lebus *et al.* described over 50% of their subjects with EAH [11]. One reason could be the different running distance. The '100 km Lauf' in Biel is shorter than the 100 miles (161 km) ultra-marathon and according to this, finishing times were also faster in the '100 km Lauf' in Biel. Ultra-marathoners required ~26 hours in Rio Del Lago compared to ~12 hours in Biel. Furthermore in the '100 km Lauf' in Biel, the temperatures were clearly lower at 15.6 °C to 21.7 °C compared with the study of Lebus *et al.* where the

temperatures were between 12.2 and 37.6 °C [11]. When the prevalence of EAH was investigated in the '100 km Lauf' across years from 2007 to 2011, seven of 145 subjects (4.8 %) developed EAH [8].

Risk factors for exercise-associated hyponatremia

Fluid overload is considered as the main risk factor in the pathogenesis of EAH [1, 6, 7, 10, 12, 13]. In these subjects, fluid intake was significantly and negatively related to both post-race serum [Na^+] and the change in serum [Na^+]. However, no subject developed EAH. Although these subjects consumed ~0.6 l of fluid per race hour, the prevalence of EAH in these 100-km ultra-marathoners was lower when compared to reports on marathoners [5, 15, 26].

Event inexperience and slow running are further risk factors for EAH [10]. In these subjects, weekly running kilometres, mean running speed during training, personal best time in a marathon and personal best time in a 100-km ultra-marathon were related to race time. Recent reports on 100-km ultra-marathoners reported that pre-race experience such as high training volume in kilometres per week, fast running speed during training and a fast personal best time in a marathon were associated with race time in a 100-km ultra-marathon [27-29]. A high training volume [28, 29] and a fast running speed while training [27-29] were highly predictive for a fast 100-km race time. We assume that these subjects were highly experienced ultra-runners which might explain why no case of EAH occurred in these athletes.

Why increased serum sodium after the ultra-marathon?

An important finding was that no ultra-runner developed EAH since both athletes with a pre-race serum [Na^+] of < 135 mmol/l also had a post-race serum [Na^+] of < 135 mmol/l. We found a significant and negative correlation between the change in body mass and post-race

serum [Na^+] (see **Figure 1**). Serum [Na^+] increased by 1.6 % and body mass decreased by 1.9 kg. This corresponds to former studies, where athletes with less weight loss (or more pronounced weight gain) had lower serum [Na^+] [3, 15, 17].

Post-race serum [Na^+] correlated significantly and negatively to fluid intake (see **Figure 2**). Ultra-runners who drank less during the race had higher post-race serum [Na^+]. With this finding we were able to support the first hypothesis of Noakes *et al.* in the pathogenesis of EAH [6]. Fluid overload and excessive drinking were supposed to lead to EAH [6, 12, 16]. Several investigators have described fluid overload, as a consequence of excessive drinking, as the main risk factor in the pathogenesis of EAH [6, 7, 10, 13, 30]. Athletes are recommended to drink between 0.4 l/h and 0.8 l/h during endurance performances [31]. Excessive drinking is especially likely to lead to EAH when exercising for more than four hours [30]. Our subjects consumed on average 0.58 (0.53;0.63) l/h. This amount corresponds to the recommendation in the 'Position Statement' of the International Marathon Medical Directors Association (IMMDA) [32]. Our ultra-marathoners in the '100 km Lauf' probably had a strict discipline in fluid ingestion even though there was a refreshment station every 5.9 km. Presumably this was because of the experience of the subjects [32].

One might assume that post-race serum [Na^+] might be related to sodium intake during the race. However, we found no correlation between both post-race serum [Na^+] and the change in serum [Na^+] with sodium intake. We can support the findings of Hew-Butler *et al.* [33] and Speedy *et al.* [34]. Hew-Butler *et al.* reported maintained serum [Na^+] between the groups with sodium or placebo supplementation and the group who had no supplementation but ate and drank normally [33]. There were no significant differences in serum [Na^+] in these groups. Speedy *et al.* found no correlations in salt supply and the change in serum [Na^+] [34]. Other studies, however, showed a correlation between particular sports drinks (Gatorade® or a

supply of sodium citrate) and serum [Na^+] [35, 36]. When athletes consumed sports drinks such as Gatorade®, the concentration in serum [Na^+] changed less when compared with the intake of tap water [36].

Endocrine regulation of serum sodium concentration?

Recent studies supposed that the hormone vasopressin was involved in the pathogenesis of EAH [2, 14]. Vasopressin physiologically reduces renal free water excretion in the presence of increased blood osmolality and is responsible for water retention [14, 20]. In case of hyponatremia and/or hypervolemia, vasopressin should be suppressed [14]. When vasopressin is released in an inappropriate manner water retention could lead to fluid overload and EAH. Siegel *et al.* [2], however, found runners with EAH and measurable vasopressin levels, whereas Speedy *et al.* [37] concluded that fluid retention was not due to increased vasopressin activity.

The activation of the renin-angiotensin-system and plasma aldosterone might be another reason for the expansion in plasma volume and water retention [19]. Fellmann *et al.* described an increased plasma volume due to sodium retention [38]. In these subjects, the change in serum [Na^+] showed a significant correlation with the change in copeptin but not with aldosterone. Based on these findings we concluded that vasopressin was positively associated with post-race serum [Na^+] in these subjects. Aldosterone could have an influence on post-race serum [Na^+] in this study because of its function of sodium conservation [13]. An older study showed constant serum [Na^+] with a significant correlation to the increase in aldosterone [19]. In contrast to this study, we found no association between post-race serum [Na^+] and increased post-race aldosterone. However, the change in aldosterone was highly significantly and positively associated with post-race change in transtubular potassium gradient and the change in potassium-to-sodium ratio in urine.

Is vasopressin involved in the pathogenesis of exercise-associated hyponatremia?

Recent investigations showed that vasopressin should be involved in developing EAH [2, 14]. Vasopressin impairs renal function for retaining fluids [14]. When vasopressin is released during exercise in an inappropriate manner there is a risk of fluid overload [14]. Physiologically, vasopressin is responsible for fluid balance [20]. When blood osmolality increased above the normal range of ~275-295 mOsmol/kg H_2O, vasopressin was released, corresponding to an osmotic regulation [20]. An increased blood osmolality is compensated by the secretion of vasopressin leading to an increased water reabsorption in the kidney [20]. Due to the increase in water permeability in the kidney, urine osmolality increases [4].

In this study, the activity of vasopressin was quantified by copeptin, the co-secreted cleavage product of a common precursor [18]. We found a significant and positive correlation between serum osmolality and the change in copeptin (see **Figure 3**). The increase in serum osmolality is explained by the increase in both serum urea and serum sodium. As a result of the change in serum osmolality, vasopressin is released [20]. This explains the increase in copeptin during the race. Vasopressin activates V_2 receptors in the collecting tubules and water reabsorption rises. As a result of this, urine osmolality also increases [4, 20]. We found a significant and positive relation of copeptin and urine osmolality (see **Figure 4**). All these correlations between copeptin and osmolalities in both serum and urine indicate a physiological secretion of vasopressin. A significant and positive correlation between the change in copeptin and the change in serum $[Na^+]$ was also found.

Fluid intake and change in body mass and plasma sodium

Finally, we found a significant correlation between fluid intake and the change in serum [Na^+], as well as between the decrease in body mass and the increase in serum [Na^+]. This finding underlines the classic hypothesis of the pathogenesis of EAH that Noakes first described [6]. Later, other investigators also supported excessive drinking and fluid overload as the main risk factor for developing EAH [12]. Due to the results of this study we can support the recommendations made by IMMDA [32] and the advice that athletes should not consume as much fluids as possible [30]. Excessive fluid retention should be avoided to prevent EAH [10, 32]. Athletes should drink *ad libitum* when they are thirsty and they should prevent weight gain during exercise [10].

To summarise, athletes with a decrease in body mass showed higher post-race serum [Na^+]. This correlates with Hew-Butlers' advice to avoid weight gain in order to prevent EAH [10]. We assume that these subjects were highly experienced ultra-marathoners, which is important for the race outcome and obviously prevented EAH, since no subject developed EAH. Serum [Na^+] increased and was significantly and negatively associated with the decrease in body mass. Fluid intake was significantly related to post-race serum [Na^+], the change in serum [Na^+] during exercise and the change in body mass. The change in copeptin was associated with the change in serum [Na^+]; aldosterone was not related to post-race serum [Na^+]. Copeptin showed a positive relation to serum and urine osmolality. Increased serum osmolality seemed to stimulate the release of vasopressin and as a result of elevated vasopressin and its influence on fluid retention urine osmolality also rose. Due to these findings we suggest that serum [Na^+] in these ultra-runners was regulated by both the mechanisms of fluid intake during exercise and the increased activity of vasopressin.

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Figure captions

Figure 1: The decrease in body mass was significantly and negatively related to post-race serum [Na^+] (n = 50) (r = - 0.36, p = 0.011)

Figure 2: Fluid intake was significantly and negatively related to post-race serum [Na^+] (n = 50) (r = - 0.34, p = 0.014)

Figure 3: Pre and post-race serum osmolality values were associated with plasma copeptin concentrations (n = 50) (r = 0.61, p < 0.001)

Figure 4: Pre and post-race urine osmolality values were associated with plasma copeptin concentrations (n = 50) (r = 0.38, p < 0.001)

Figure 5: Pre and post-race urine potassium-to-sodium ratios were significantly associated with plasma aldosterone concentrations (n = 50) (r = 0.85, p < 0.001).

Figure 6: Urine excretion rates before, during and after the race. Mean values (95% Confidence intervals). * p<0.001 vs. pre-race. Fluid intake during the race was 8.1 (7.3;8.9)) $ml \cdot h^{-1} \cdot kg^{-1}$.

	n	*mean*	*(CI 95%)*
Age (years)	50	47.8	(45.4;50.3)
Body height (m)	50	1.79	(1.77;1.81)
Body mass (kg)	50	74.9	(72.2;77.7)
Body mass index (kg/m^2)	50	23.3	(22.6;23.9)
Experience as ultra-runner (years)	50	11.8	(9.6;14.1)
Training volume (hrs/week)	50	8.6	(5.6;11.7)
Training volume (km/week)	50	66.5	(58.7;74.4)
Training speed (km/h)	50	10.7	(10.3;11.1)
Marathons finished (number)	48	33	(17.4;48.7)
100 km races finished (number)	35	3.9	(2.4;5.4)
Marathon personal best time (hr:min)	48	03:31	(03:22;03:40)
100 km race personal best time (hr:min)	35	11:22	(10:41;12:03)

Table 1: Characteristics of the subjects. Results are presented as mean and 95% CI.

	Pre race*	Post race*	Percent change*	Significance†
Body mass (kg)	74.9 (72.2;77.7)	73.0 (70.3;75.7)	-2.5 (-3.1;-2.1)	<0.0001
Plasma copeptin (pmol/l)	6.4 (5.5;7.4)	75.0 (50.4;99.6)	1,212 (795;1,628)	<0.0001
Plasma aldosterone (ng/l)	90 (79;102)	424 (351;496)	454 (333;575)	<0.0001
Haemoglobin (g/dl)	14.5 (14.3;14.8)	14.5 (14.2;14.8)	-0.4 (-1.6;0.9)	
Haematocrit (%)	43.5 (42.7;44.2)	43.3 (42.5;44.2)	0.3 (-1.6;1.0)	
Serum sodium (mmol/l)	136.6 (135.4;136.7)	138.2 (137.6;138.9)	1.6 (1.0;2.2)	<0.0001
Serum potassium (mmol/l)	4.1 (4.0;4.2)	4.3 (4.2;4.4)	3.9 (0.1;7.7)	
Serum glucose (mmol/l)	5.3 (5.0;5.6)	5.4 (5.1;5.8)	7.1 (-1.8;16.1)	
Serum creatinine (umol/l)	77.8 (74.5;81.1)	100.4 (93.3;107.5)	30.1 (21.1;39.2)	<0.0001
Serum urea (mmol/l)	5.7 (5.4;6.0)	9.1 (8.4;9.8)	61.5 (49.5;73.6)	<0.0001
Serum osmolality (mosmol/kgH_2O)	296.4 (295.1;297.6)	302.0 (299.9;304.1)	1.9 (1.2;2.7)	<0.0001
Urine specific gravity (g/ml)	1.017 (1.015;1.019)	1.026 (1.015;1.028)	0.93 (0.72;1.1)	<0.0001
Fractional sodium excretion (%)	0.918 (0.816;1.021)	0.381 (0.281;0.460)	-506 (-66.7;-34.6)	<0.0001
Fractional potassium excretion (%)	0.114 (0.098;0.129)	0.191 (0.168;0.214)	100 (64;136)	<0.0001
Fractional urea excretion (%)	52.7 (49.1;56.4)	31.0 (26.8;35.1)	-39.0 (-47.7;-30.2)	<0.0001
Fractional osmolar excretion (%)	0.022 (0.020;0.023)	0.017 (0.015;0.018)	-18.7 (-27.7;-9.7)	<0.0001
Transtubular potassium gradient (ratio)	28.3 (21.8;34.8)	99.7 (84.9;114.6)	828 (378;1278)	<0.0001

* *n*=50, mean value, CI 95%
†= by paired T-test

Table 2: Results of the physical, haematological and urinary parameters before and after the race.

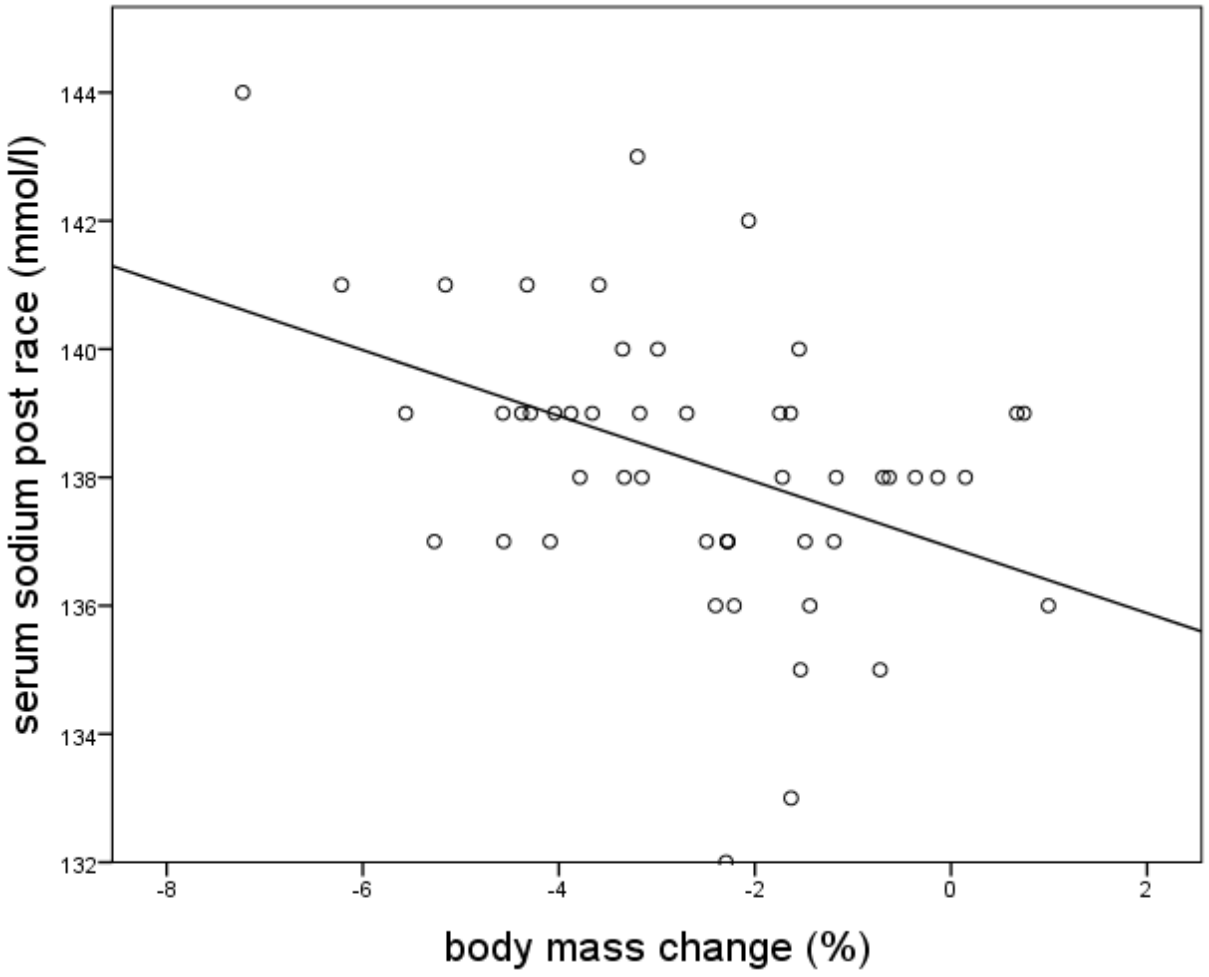
serum sodium post race (mmol/l)
144
142
140
138
136
134
132
-8
-6
-4
-2
0
2
body mass change (%)

Figure 1

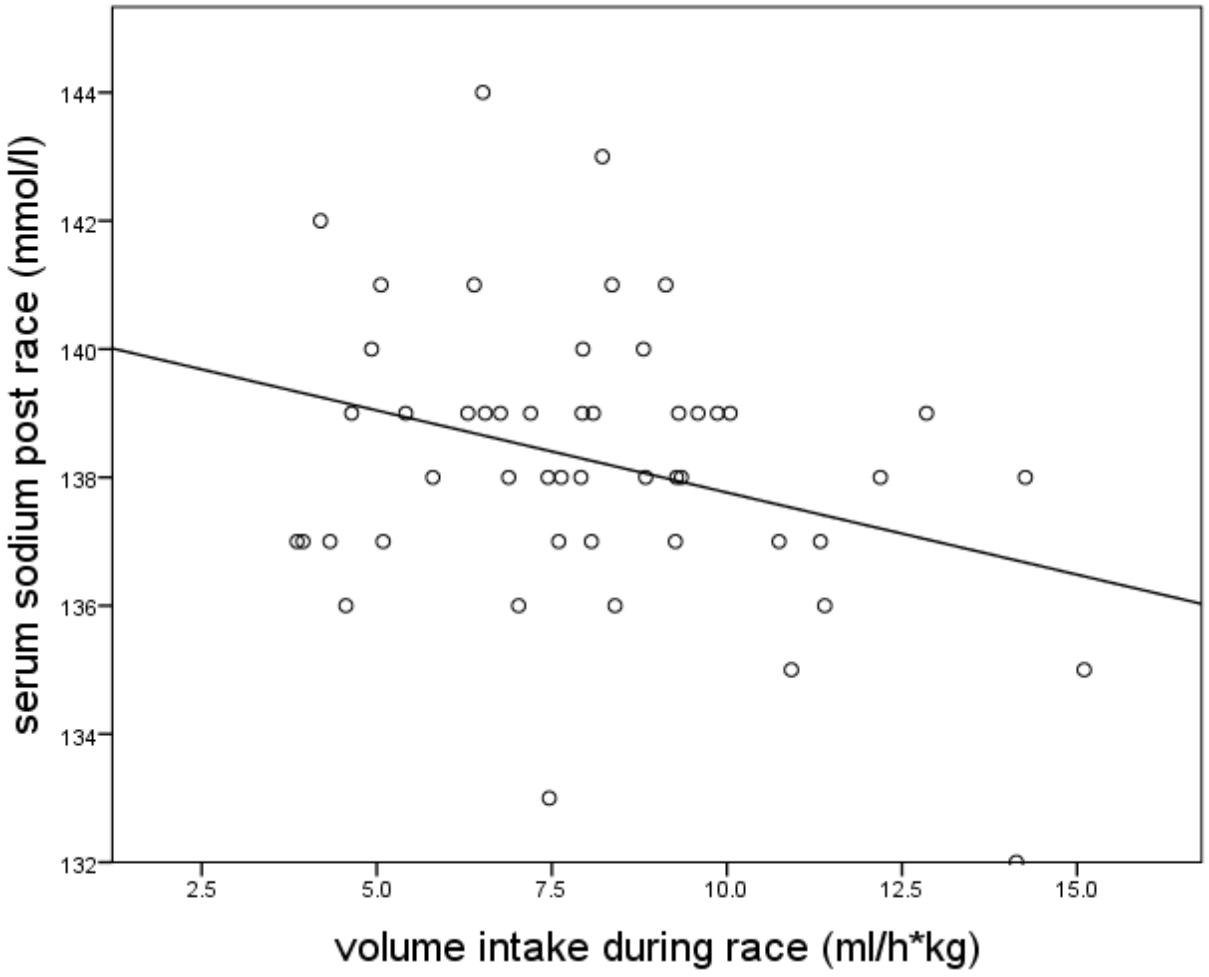
serum sodium post race (mmol/l)
144
142
140
138
136
134
132
2.5
5.0
7.5
10.0
12.5
15.0
volume intake during race (ml/h*kg)

Figure 2

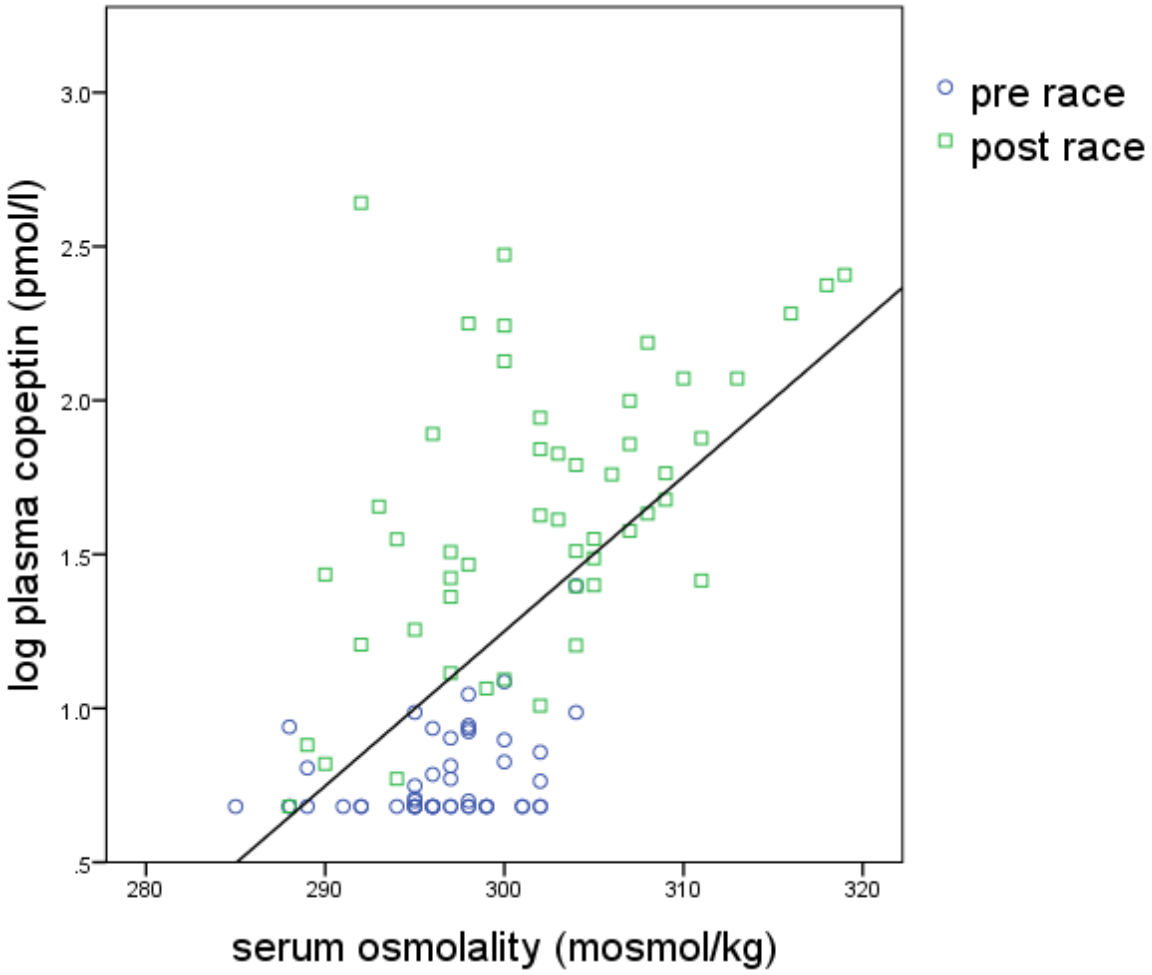
log plasma copeptin (pmol/l)
3.0
2.5
2.0
1.5
1.0
.5
280
290
300
310
320
serum osmolality (mosmol/kg)
pre race
post race

Figure 3

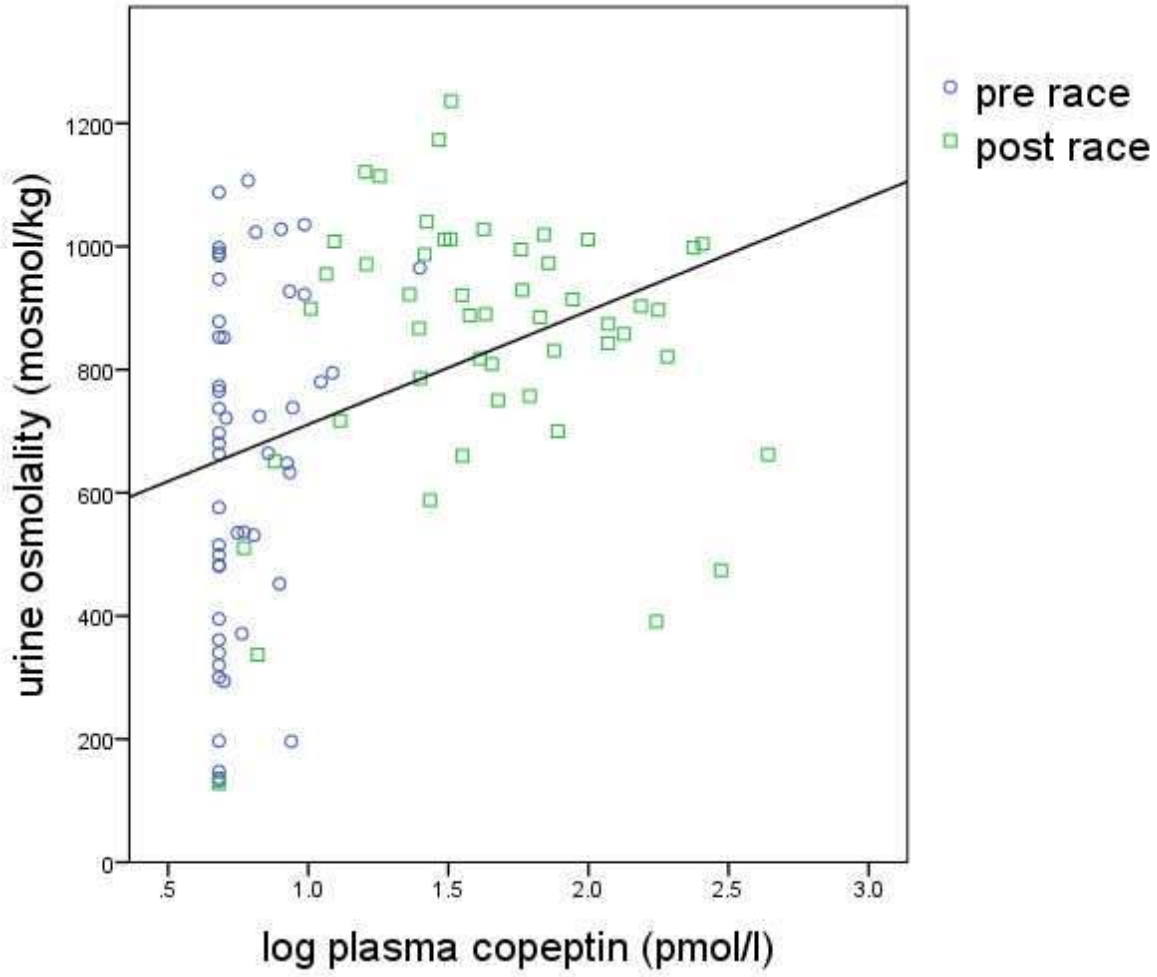
pre race
post race
urine osmolality (mosmol/kg)
1200
1000
800
600
400
200
0
.5
1.0
1.5
2.0
2.5
3.0
log plasma copeptin (pmol/l)

Figure 4

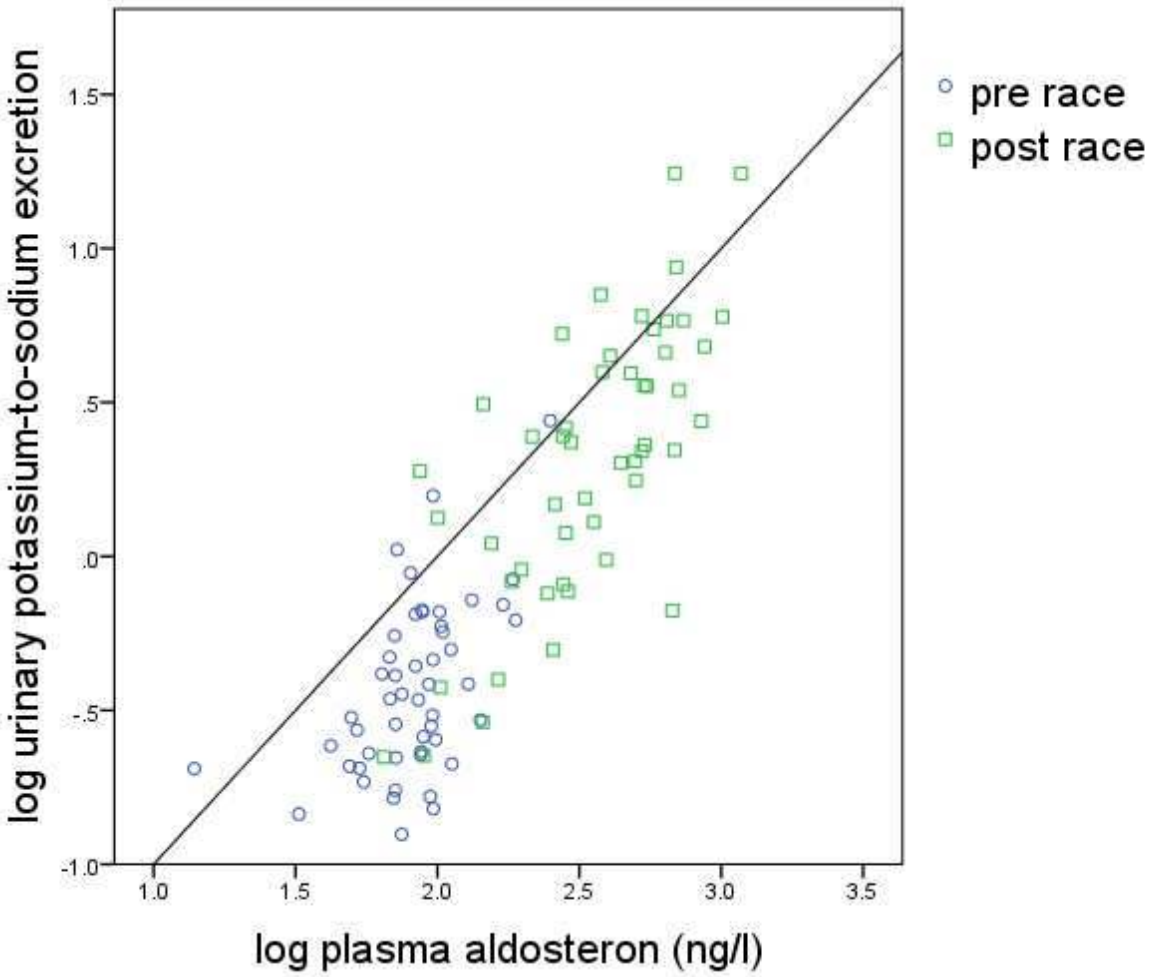
log urinary potassium-to-sodium excretion
1.5
1.0
.5
.0
-.5
-1.0
1.0
1.5
2.0
2.5
3.0
3.5
log plasma aldosteron (ng/l)
pre race
post race

Figure 5

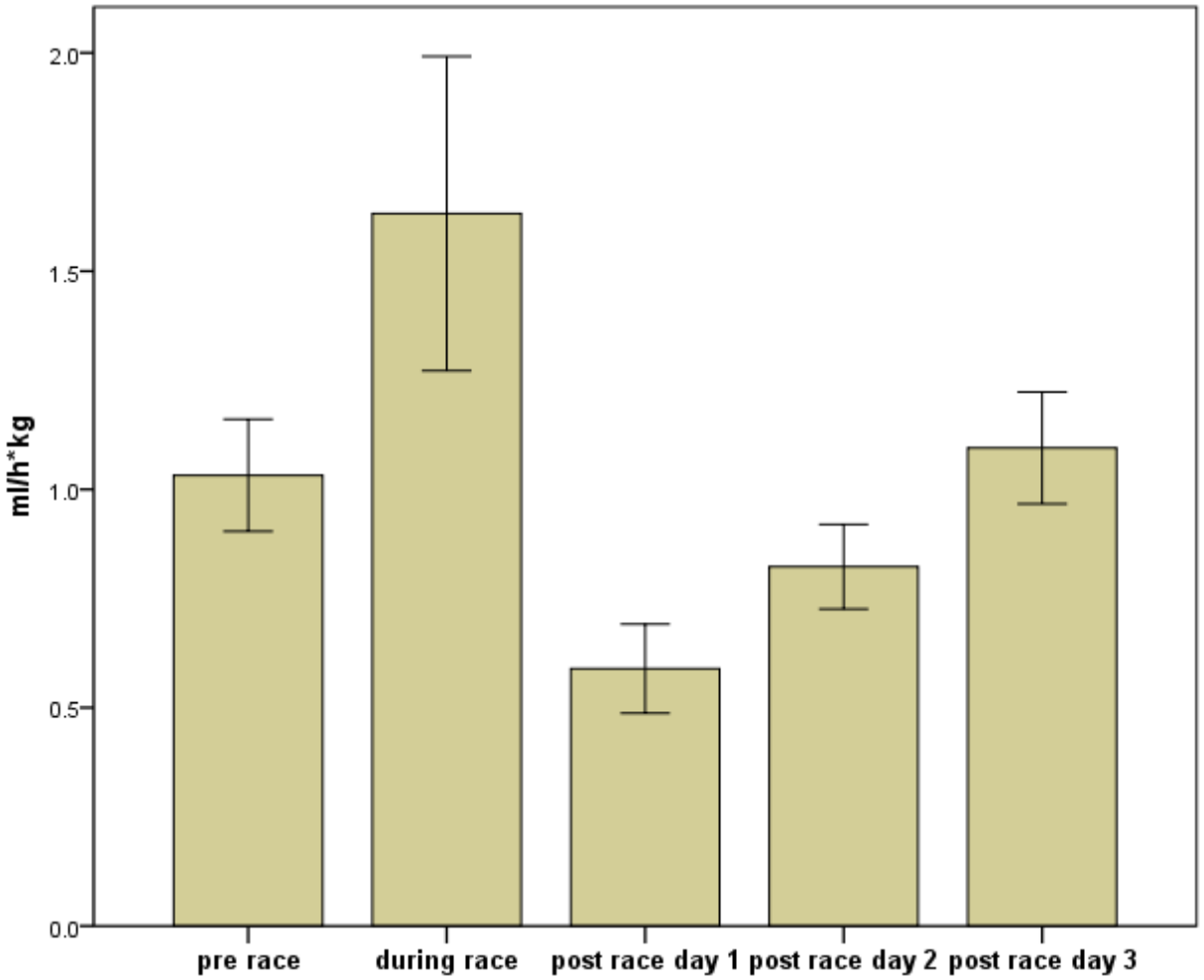
2.0
1.5
1.0
0.5
0.0
ml/h*kg
pre race
during race
post race day 1
post race day 2
post race day 3

Figure 6